Intellectual Property for Crop Transformation: A Continuing Saga for Agricultural Innovation in the Public Sector

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Figure 1 shows Cohen and Boyer's fundamental recombinant-DNA patent, issued in 1980. They were founders of the startup company Genentech. The patent was managed by Stanford and the University of California together. In a climate like today's, it might have been licensed exclusively to Genentech. If it had, how many biotech companies would there now be?: one! In California alone, there are 1,600. This was licensed on a non-exclusive basis for a very nominal charge. Such enabling technologies can support entire industries if they are widely available; otherwise, they support a very narrow base.

Figure 2 provides a snapshot of the intellectual-property landscape in agricultural biotechnology a few years ago. Pie A shows the landscape across the patent office as a whole, with approximately 2.5 percent assigned to the public sector. Pie B shows a very different landscape for ag-biotech, with a few large players with large intellectual-property portfolios. It has been speculated that the management of these intellectual-property portfolios has played a part in producing an industry that is relatively concentrated in a few players. Another different feature is that there is a large public-sector slice in Pie B, which is highly fragmented across universities (Pie C).

This gave rise to the formation the Public Intellectual Property Resource for Agriculture (PIPRA[1]) by the Rockefeller Foundation: could it take this public-sector portfolio and do something interesting with it—use it in strategic ways to enable not only the public sector but enable industries also?

[1]PIPRA enables access to public innovation. PIPRA supports innovation in agriculture, health, water, and energy technologies. In collaboration with 50+ universities and research centers and a pro bono attorney network, PIPRA provides intellectual property rights and commercialization-strategy services to increase the impact of public-sector innovation, particularly for developing countries and specialty markets.

United States Patent [19] [11] **4,237,224**

Cohen et al. [45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

Figure 1. Cohen and Boyer's landmark patent for "producing biologically functional molecular chimeras."

The first thing that the Rockefeller Foundation asked of PIPRA was to look at enabling technologies—the vectors, promoters, selectable markers, transformation methods, including *Agrobacterium*, that can link novel traits with good germplasm. The request from the Rockefeller Foundation was to examine the public-sector portfolio to see if we could create something that has freedom to operate and could be widely used.

We started the process at the Danforth Center in St. Louis. The panel of experts who met comprised plant biologists and lawyers. The objective was to define applicable technical, legal and regulatory design parameters, similar to a standard-setting process that would be used in forming a patent pool in the electronics industry. The criteria drawn up included:

- *Agrobacterium*-mediated was preferred
- A wide range of promoters
- Clear of intellectual property (IP) blocks in the United States and elsewhere (the most essential feature)
- Plant products should be marker-free
- Desirable to have the possibility of "all plant" integrations.

We went through a process of gathering freedom-to-operate opinions from an attorney network who contributed their time on a *pro bono* basis, and then to define terms of technology and corporation into a patent pool. We formed a patent pool around these technologies, developed a transformation system, and published it (Chi-Ham *et al.*, 2012). It has been distributed to a number of public-research institutions in the United

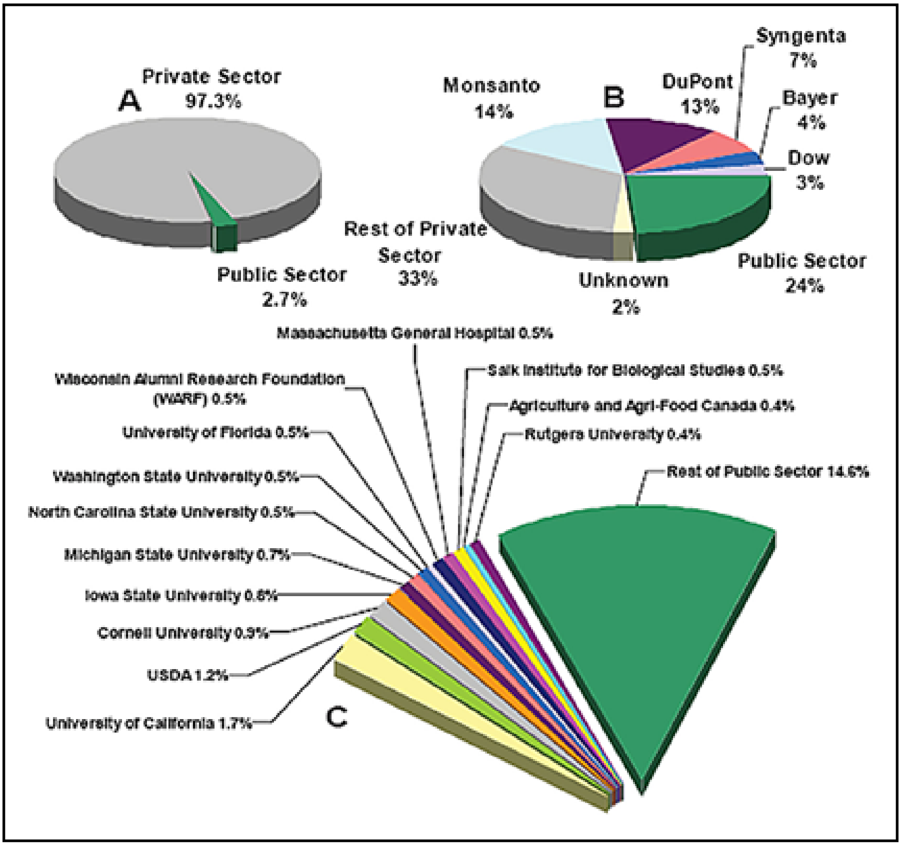


Figure 2. Recent intellectual property landscape in agricultural biotech.

States and internationally as well as to companies. Currently, it is the basis for seven trait incorporations: three that are essentially humanitarian products for Africa funded by USAID, and four commercial traits. Furthermore, the system has been used to generate a number of commercial events that are now in later-stage field-testing.

As mentioned, the published transformation system is *Agrobacterium*-based, an aspect on which the landscape has changed. Figure 3 shows the timeline of a broad and important patent application on *Agrobacterium*, filed in 1983 not only in the United States but in many other countries as well. At that particular time, in the rest of the world, patents expired 20 years after application. So, in the rest of the world this patent has expired. However, in the United States under the pre-1995 law, patents have a term of 17 years from issuance, and so it will be in force in the United States until 2029.

When we developed these vectors, it was during a period when there were no broad *Agrobacterium* patents. The ones that had existed had expired and this particular one had

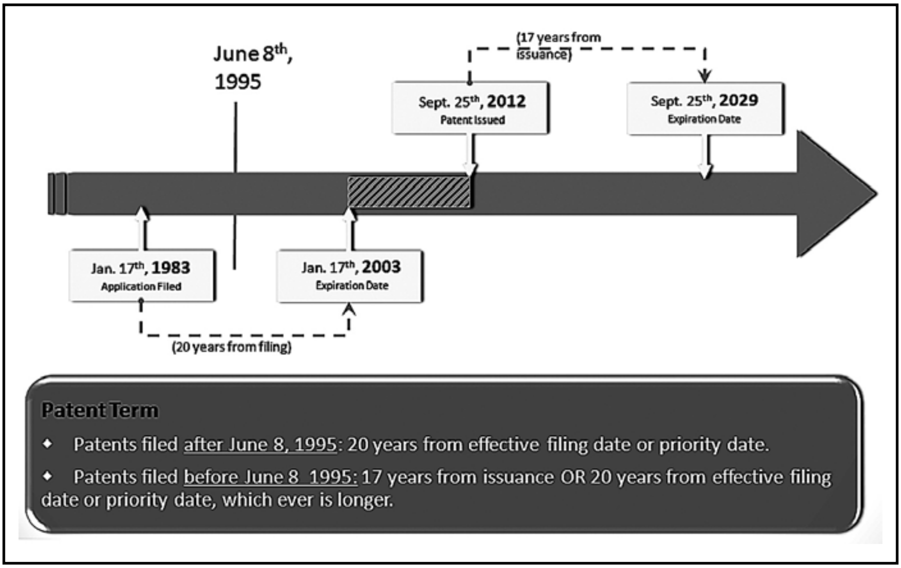


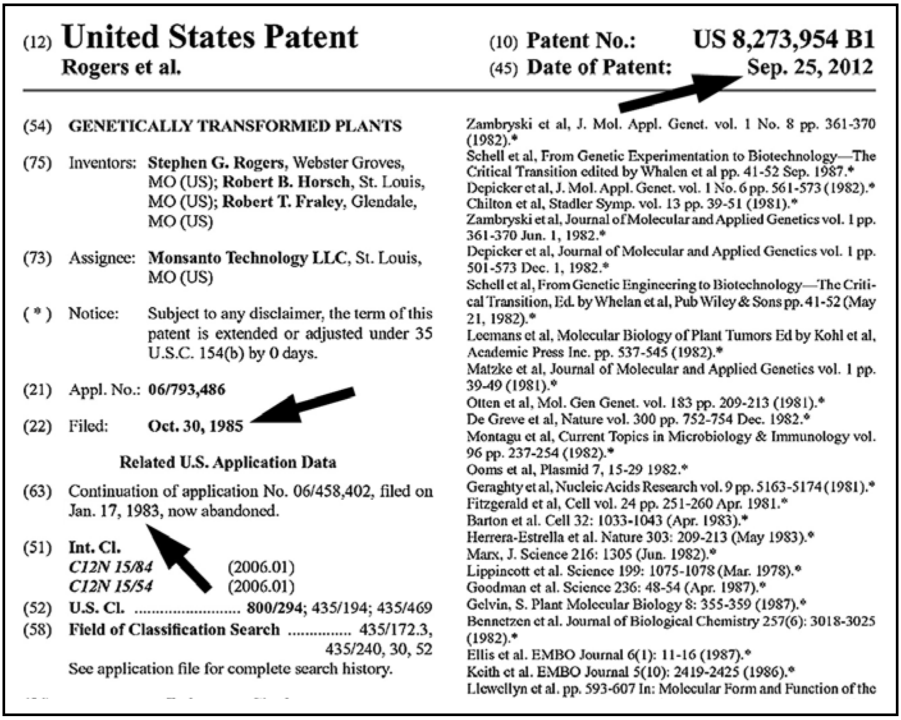
Figure 3. Over 29 years of prosecution. Anticipated expiration date: September 25, 2029.

not yet been issued. And so, this is where the landscape has changed. This very broad, well deserved, patent was issued to Monsanto on September 25, 2012 (Figure 4): *Genetically Transformed Plants*. Filed originally in 1985 as a continuation of an application filed in1983, the patent was issued in 2012, and, as discussed above, will stay in force until 2029. University researchers who use *Agrobacterium* to transform dicots are infringing on this patent. On the other hand, Monsanto is offering a free license to academic institutions to use this methodology, which they intend to enforce. Infringing researchers are likely to hear from Monsanto. This raises the issue of the terms of that license. In fact, the conditions are reasonable and we have been working with Monsanto to improve them.

Figure 5 shows the scope of claims. It talks about genetically-transforming dicots by contact with *Agrobacterium* and incorporating *Agrobacterium* T-DNA borders; so, it's very broad.

Inventing Around

The broad coverage (Figure 6, arrowed fields) has prompted examination of prospects to "invent around" (Figure 6, "X"). There may be opportunities to replace *Agrobacterium* with other bacterial genera. It talks about T-DNA from *Agrobacterium*. This suggests there may be opportunities to invent around utilizing either P-DNA or, potentially, synthetic borders. In fact, alternatives to *Agrobacterium* have been pursued for some time. In 2005, Richard Jefferson and colleagues published a paper and filed patents on using *Rhizobium* species to harbor a Ti plasmid for delivery of transgenes to plants (Figure 7). This was



(12) **United States Patent**
Rogers et al.

(10) **Patent No.: US 8,273,954 B1**
(45) **Date of Patent: Sep. 25, 2012**

(54) **GENETICALLY TRANSFORMED PLANTS**

(75) Inventors: **Stephen G. Rogers**, Webster Groves, MO (US); **Robert B. Horsch**, St. Louis, MO (US); **Robert T. Fraley**, Glendale, MO (US)

(73) Assignee: **Monsanto Technology LLC**, St. Louis, MO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **06/793,486**

(22) Filed: **Oct. 30, 1985**

Related U.S. Application Data

(63) Continuation of application No. 06/458,402, filed on Jan. 17, 1983, now abandoned.

(51) **Int. Cl.**
C12N 15/84 (2006.01)
C12N 15/54 (2006.01)

(52) **U.S. Cl.** **800/294**; 435/194; 435/469

(58) **Field of Classification Search** 435/172.3, 435/240, 30, 52
See application file for complete search history.

Zambryski et al, J. Mol. Appl. Genet. vol. 1 No. 8 pp. 361-370 (1982).*
Schell et al, From Genetic Experimentation to Biotechnology—The Critical Transition edited by Whalen et al pp. 41-52 Sep. 1987.*
Depicker et al, J. Mol. Appl. Genet. vol. 1 No. 6 pp. 561-573 (1982).*
Chilton et al, Stadler Symp. vol. 13 pp. 39-51 (1981).*
Zambryski et al, Journal of Molecular and Applied Genetics vol. 1 pp. 361-370 Jun. 1, 1982.*
Depicker et al, Journal of Molecular and Applied Genetics vol. 1 pp. 501-573 Dec. 1, 1982.*
Schell et al, From Genetic Engineering to Biotechnology—The Critical Transition, Ed. by Whelan et al, Pub Wiley & Sons pp. 41-52 (May 21, 1982).*
Leemans et al, Molecular Biology of Plant Tumors Ed by Kohl et al, Academic Press Inc. pp. 537-545 (1982).*
Matzke et al, Journal of Molecular and Applied Genetics vol. 1 pp. 39-49 (1981).*
Otten et al, Mol. Gen Genet. vol. 183 pp. 209-213 (1981).*
De Greve et al, Nature vol. 300 pp. 752-754 Dec. 1982.*
Montagu et al, Current Topics in Microbiology & Immunology vol. 96 pp. 237-254 (1982).*
Ooms et al, Plasmid 7, 15-29 1982.*
Geraghty et al, Nucleic Acids Research vol. 9 pp. 5163-5174 (1981).*
Fitzgerald et al, Cell vol. 24 pp. 251-260 Apr. 1981.*
Barton et al. Cell 32: 1033-1043 (Apr. 1983).*
Herrera-Estrella et al. Nature 303: 209-213 (May 1983).*
Marx, J. Science 216: 1305 (Jun. 1982).*
Lippincott et al. Science 199: 1075-1078 (Mar. 1978).*
Goodman et al. Science 236: 48-54 (Apr. 1987).*
Gelvin, S. Plant Molecular Biology 8: 355-359 (1987).*
Bennetzen et al. Journal of Biological Chemistry 257(6): 3018-3025 (1982).*
Ellis et al. EMBO Journal 6(1): 11-16 (1987).*
Keith et al. EMBO Journal 5(10): 2419-2425 (1986).*
Llewellyn et al. pp. 593-607 In: Molecular Form and Function of the

Figure 4. Recently issued patent.

the basis of what he called BiOS or open-innovation platform. However, efficiency was low and the concept failed to gain traction.

In 2011, a group in Ireland (led by Ewen Mullins) published on and patented *Ensifer adhaerens*—closely related to the *Rhizobium/Agrobacterium* group—claiming broad applicability for gene transfer. Figure 8 includes data generated with potato.

Another area to invent around is P-DNA or synthetic DNA borders (Figure 6), which has been the topic of important publications (Figure 9). Because we keep a watch on these things, we have noticed that one of the seminal papers on this topic has been retracted, which may affect the patent. If these move into the public domain, they would probably constitute a complete workaround.

Other PIPRA Activities

PIPRA provides intellectual property support to a number of agencies and universities. One the reasons that the Rockefeller Foundation became interested in intellectual property was the Golden Rice story and the intellectual property audit that identified a large number of proprietary technologies that were infringed (Figure 10). Ingo Potrykus agrees

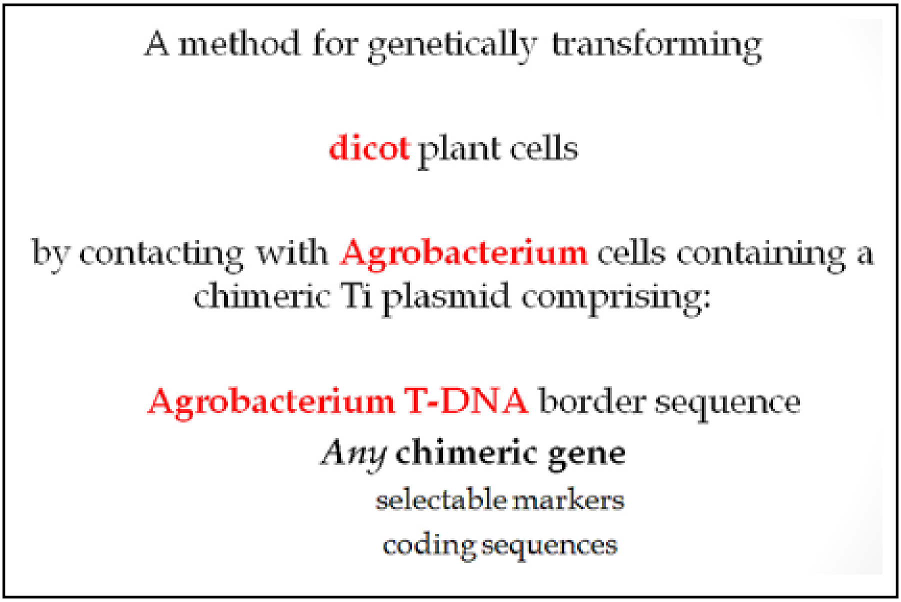


Figure 5. Patent No. 8273954, Genetically Transformed Plants: Scope of claims.

with Dennis Gonsalves[2] that intellectual property was not the main issue preventing the advancement of this innovation. In spite of the large number of proprietary technologies involved, it was quickly realized that Golden Rice could be "rebuilt" using approximately five proprietary technologies instead of seventy. As suggested by Scott Thenell[3] regarding planning innovations to address regulatory issues, forethought may also minimize intellectual property issues. PIPRA makes a lot of freedom-to-operate assessments for public-sector projects to determine if products or processes use third-party proprietary technologies and, if so, can the project obtain the rights to those properties? We look at intellectual property landscapes and patents, but we also look at materials used and material transfer agreements, which, it turns out, are always the more problematic.

Anyone who has used a Gateway vector has agreed to the conditions set out in Figure 11. This license says that the buyer cannot sell or otherwise transfer materials made using this product or its components to a third party or for any commercial purposes.

Figure 12 provides a list of about half of our freedom-to-operate (FTO) assessments, many of which were for the Bill and Linda Gates Foundation. Others were for the Department of Energy, which is now involved in a number of projects. The common feature of these projects is that they are funding research with commercial intentions. The agencies, of course, are interested in basic findings but they also want to see products that solve real problems. As a result, they've gotten quite involved in looking at FTO assessments before the research starts, *i.e.* addressing up-front issues and minimizing downstream issues in these particular projects.

[2]Pages 37–46.
[3]Pages 183–194.

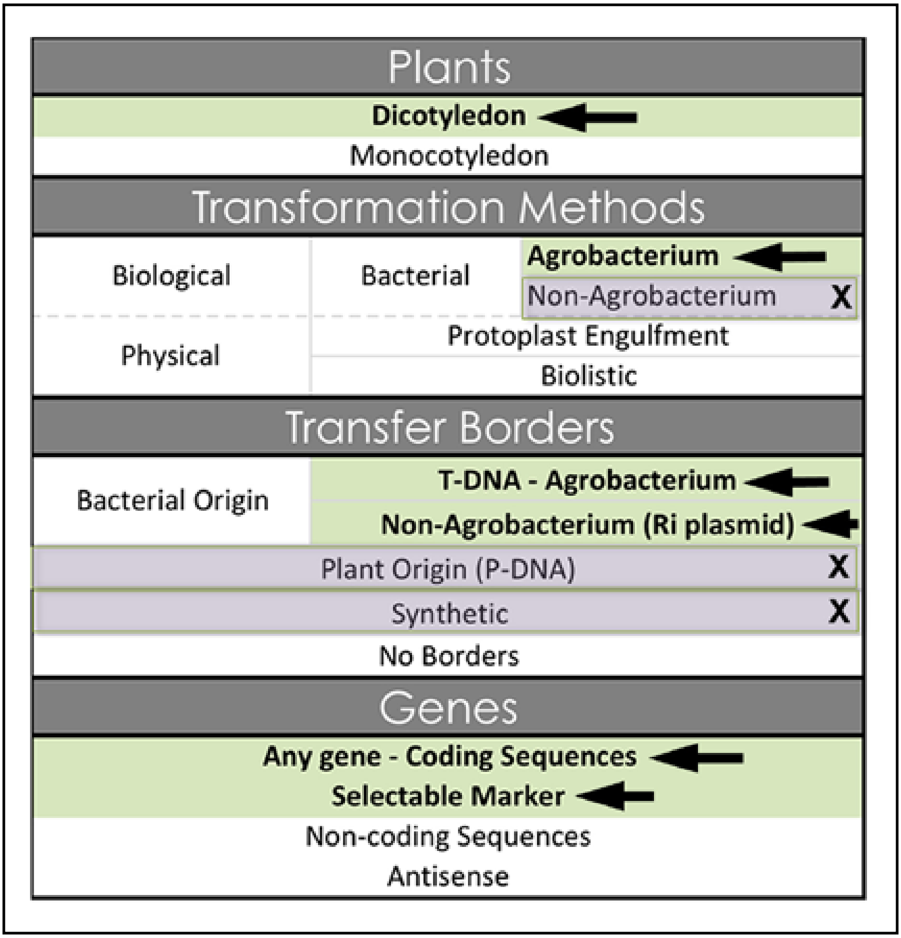


Figure 6. Preliminary analysis: Scope of claims.
Inventing Around

Education and Outreach

Another area of PIPRA involvement is education and outreach. Figure 13 shows a two-volume set of *Best Practices* handbooks that we published in 2007. We run a licensing academy for technology managers from developing countries. The academy currently has forty students from twenty countries. There is great interest and significant hunger in understanding how to manage intellectual property in developing countries. Accordingly, awareness is increasing. A lot of countries are focusing on increasing their capacity so that they can address their own innovations. Not only are they interested in using our innovations, but they want to protect and exploit their own.

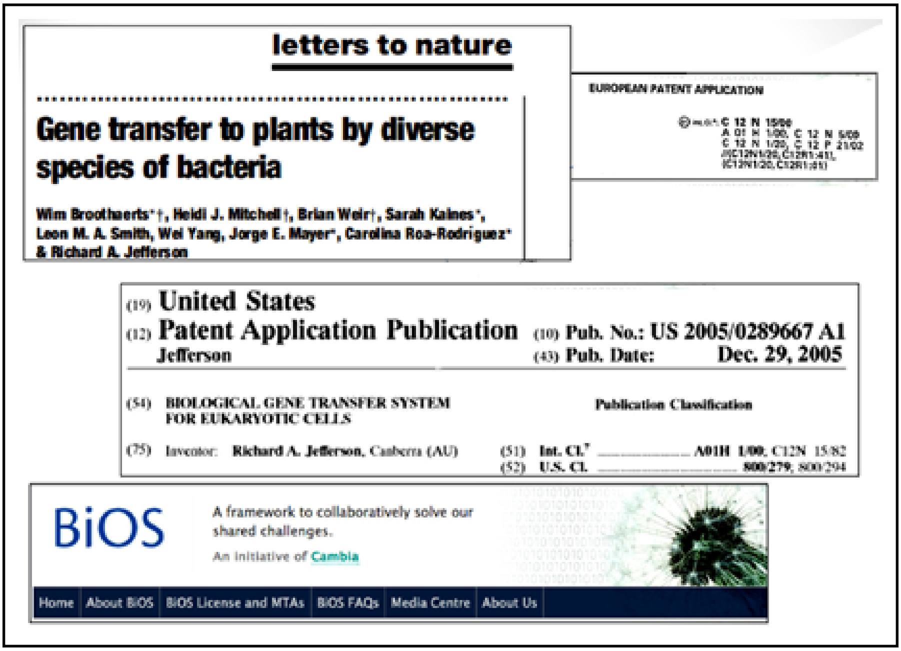


Figure 7. Alternatives to *Agrobacterium* for gene delivery.

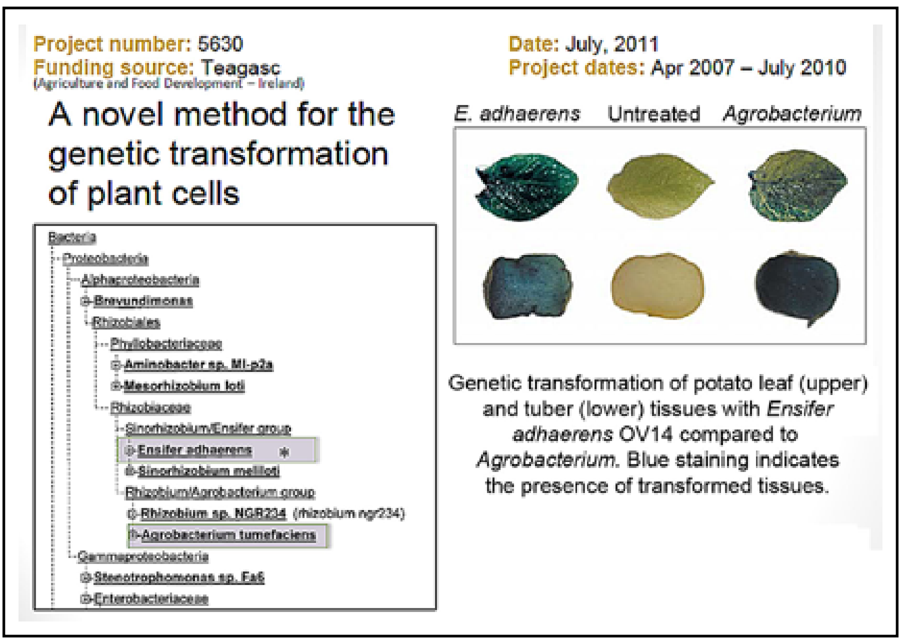


Figure 8. Transformation of potato with *Ensifer adhaerens*.

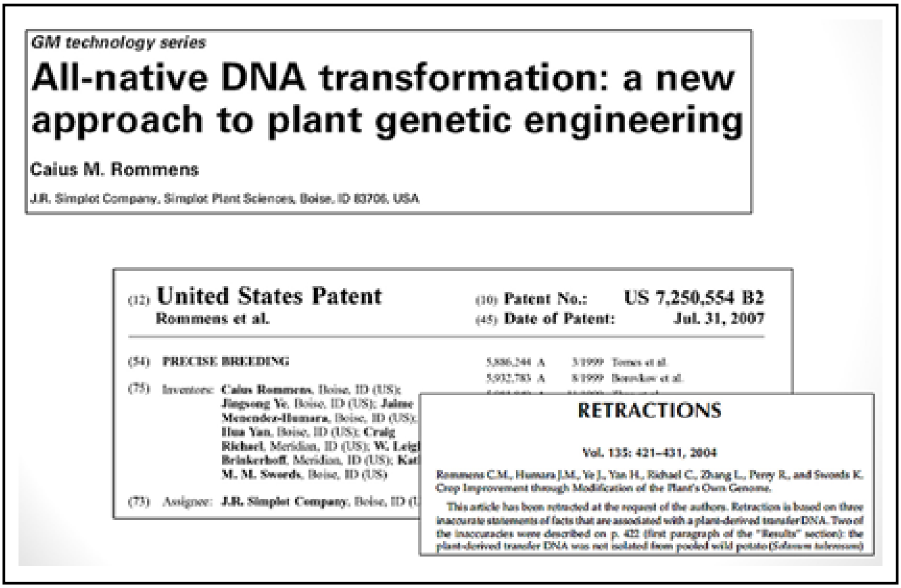


Figure 9. T-DNA replacement with "P-DNA" or synthetic DNA borders.

Figure 10. Intellectual property creates challenges for public research and missed opportunities for crop development.

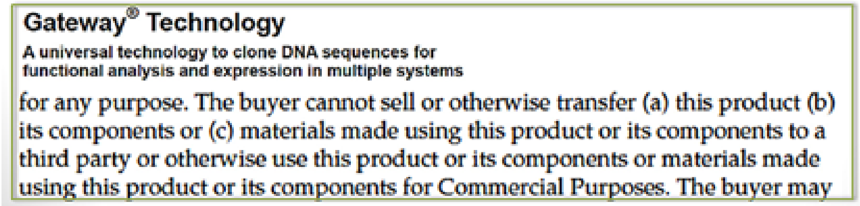

Gateway® Technology
A universal technology to clone DNA sequences for functional analysis and expression in multiple systems
for any purpose. The buyer cannot sell or otherwise transfer (a) this product (b) its components or (c) materials made using this product or its components to a third party or otherwise use this product or its components or materials made using this product or its components for Commercial Purposes. The buyer may

Figure 11. A "shrink wrapped" license.

Gene Patents

PIPRA is involved in a few genome projects and the issues of gene patents. Patent claims are appropriating public science at a fast pace. Figure 14 shows a famous patent application, sometimes referred to as "the patent from hell." This is a claim for a transgenic plant having an improved trait by expressing any of these genes or any related gene with 65 percent homology. These are sometimes called "jumbo" patents.

Figure 15 illustrates the situation for *Arabidopsis*- and rice-gene patents. Those in blue (88) are patents that were issued before the public release of the *Arabidopsis* genome. Four hundred and forty patents were issued on *Arabidopsis* genes after the public release of the genome. The same applies for rice: 284 before and 832 after. This raises the issue of the implications of public release of a genome, *i.e.* putting data on the Internet that provides opportunities for appropriating gene ownership.

Genome Projects

PIPRA has been working with the cacao-genome project and will be working with other similar projects soon. The cacao genome sequence was completed a few years ago for the express purpose of making it publicly available. And so, the sponsors of this genome asked PIPRA what it means to be publicly available. We worked with them to develop a portal for this genome, which involves an information access agreement with terms and conditions:

> *The user shall not claim legal ownership over the information and data. And the user agrees not to claim any sequences in any patent application. On the other hand, the foregoing shall not prevent the user from releasing, reproducing, seeking intellectual property protection on improved seeds or plants that are developed using this information.*

The goal is to protect upstream information that can be thought of as research tools and enabling technologies to ensure that they remain publicly available and focus on protection, commercialization and exploitation of downstream products for purposes of making such seeds or plants available to farmers for cultivation.

A large multi-sponsored project is on-going to sequence the genomes of some one hundred orphan crops in Africa, with the intent of using similar portals. These all may become moot points considering that the Supreme Court may disallow patenting of genes and other naturally occurring molecules. Patenting of cDNAs and the like, which don't occur in nature, may be allowed.

Patent Landscape for Strategies to address Pierce's Disease in Grapes	California Department of Food and Agriculture	3 x HIV vaccine patent landscape reports	International AIDS Vaccine Initiative
Patent Landscapes for Disease Resistant Traits in Cassava	**Bill and Melinda Gates Foundation** Donald Danforth Plant Science Center (DDPSC), the International Institute of Tropical Agriculture (IITA)	Lignocellulosic Ethanol patent landscape report	US Department of Energy
Patent Landscapes for Disease Resistant Traits in Cassava	**Bill and Melinda Gates Foundation** Donald Danforth Plant Science Center (DDPSC), the National Crop Resources Research Institute (NaCRRI), and the Kenya Agricultural Research Institute (KARI).	Stem Cell	PIPRA sponsored
Patent Landscapes for Double Haploid in Cassava	**Bill and Melinda Gates Foundation** International Center for Tropical Agriculture (CIAT), the International Institute of Tropical Agriculture (IITA), and the Shanghai Center for Cassava Biotechnology	HIV vaccine Upstream Technologies	PIPRA sponsored
Patent Landscapes for Disease Resistant Traits in Sweet Potato	**Bill and Melinda Gates Foundation** International Potato Center (Peru)	Core Technologies of four research strategies for Increase Carbon Fixation	US Department of Energy - Advanced Research Projects Agency-Energy (ARPA E); LBL, U Mass, NCSU
Patent Landscapes for Disease Resistant Traits in Wheat	**Bill and Melinda Gates Foundation** collaborative project with the University of California Davis (UC Davis), and a laboratory at the USDA in Albany, California.	Global Agricultural Patent Landscape **(See Annex A)**	Rockefeller Foundation
Patent Landscapes for Nutrition Improvement in Banana	**Bill and Melinda Gates Foundation** collaborative project with Queensland University of Technology (QUT) in Australia with the National Agricultural Research Organization (NARO) in Uganda.	4 x agricultural biotechnology	Rockefeller Foundation
Freedom to Operate Analysis on Ensifer-mediated Transformation Technology	Teagasc: The Agriculture and Food Development Authority in Ireland	Sweet Potato for Africa	Howard G. Buffet Foundation

Figure 12. Freedom to operate—project assessment/enablement.

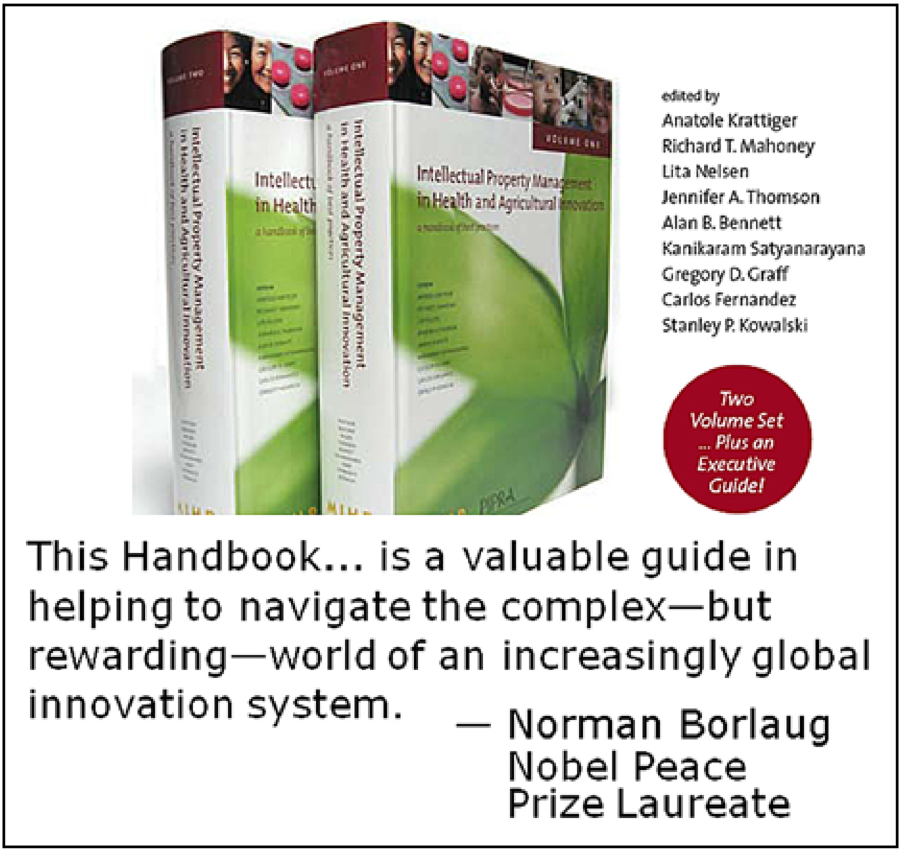


Figure 13. *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices.*

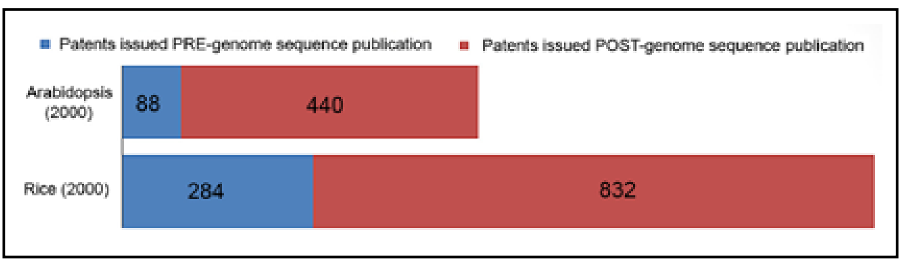


Figure 15. Number of US patents with word arabidopsis or rice in claims.

1.A transgenic plant having an improved trait relative to a control plant, wherein: (a) the transgenic plant comprises a recombinant polynucleotide encoding a first polypeptide having a conserved domain at least 65% identical to the conserved domain of a second polypeptide selected from the group consisting of SEQ ID NO: 110, 112, 116, 120, 124, 128, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 191, 195, 199, 203, 207, 211, 215, 219, 223, 227, 231, 235, 239, 243, 247, 251, 255, 259, 263, 267, 271, 275, 280, 284, 288, 292, 296, 299, 303, 306, 309, 313, 317, 321, 325, 329, 333, 337, 341, 345, 349, 353, 357, 361, 365, 369, 373, 377, 381, 385, 389, 393, 397, 401, 404, 406, 409, 413, 416, 419, 422, 425, 428, 431, 435, 439, 443, 447, 451, 454, 458, 462, 465, 468, 471, 475, 478, 482, 485, 489, 493, 497, 501, 505, 509, 512, 515, 519, 522, 526, 530, 534, 538, 542, 546, 550, 553, 557, 561, 565, 568, 571, 574, 577, 581, 585, 588, 591, 594, 597, 601, 605, 609, 613, 616, 620, 624, 628, 632, 636, 640, 644, 648, 652, 656, 660, 664, 667, 671, 674, 678, 682, 686, 689, 692, 696, 700, 704, 708, 712, 715, 719, 723, 727, 731, 734, 738, 741, 745, 749, 752, 756, 760, 762, 766, 770, 774, 778, 782, 786, 789, 793, 797, 801, 805, 809, 813, 816, 819, 823, 827, 831, 835, 839, 843, 847, 851, 855, 859, 863, 867, 871, 874, 878, 882, 886, 890, 894, 898, 901, 905, 909, 913, 917, 921, 925, 929, 933, 937, 941, 945, 949, 953, 957, 960, 963, 966, 970, 973, 976, 980, 984, 988, 992, 995, 999, 1003, 1007, 1011, 1015, 1019, 1023, 1027, 1031, 1037, 1041, 1045, 1049, 1052, 1056, 1060, 1064, 1067, 1071, 1075, 1078, 1081, 1085, 1089, 1093, 1097, 1101, 1104, 1108, 1112, 1116, 1120, 1123, 1126, 1130, 1134, 1138, 1142, 1145, 1148, 1151, 1154, 1157, 1161, 1165, 1169, 1173, 1177, 1181, 1185, 1188, 1192, 1195, 1199, 1203, 1207, 1211, 1215, 1219, 1222, 1226, 1229, 1233, 1236, 1240, 1243, 1247, 1251, 1254, 1258, 1262, 1266, 1269, 1273, 1277, 1281, 1285, 1289, 1293, 1297, 1300, 1304, 1308, 1311, 1314, 1318, 1322, 1326, 1330, 1334, 1338, 1342, 1346, 1350, 1354, 1358, 1361, 1365, 1369, 1372, 1376, 1380, 1384, 1388, 1392, 1396, 1400, 1404, 1408, 1411, 1415, 1419, 1423, 1427, 1431, 1435, 1439, 1443, 1446, 1449, 1452, 1455, 1459, 1463, 1467, 1470, 1474, 1477, 1481, 1488, 1492, 1495, 1499, 1503, 1507, 1511, 1515, 1519, 1522, 1526, 1530, 1533, 1537, 1541, 1545, 1549, 1553, 1557, 1561, 1565, 1568, 1572, 1576, 1579, 1583, 1586, 1589, 1593, 1596, 1598, 1602, 1604, 1608, 1611, 1614, 1617, 1620, 1624, 1628, 1632, 1636, 1640, 1645, 1648, 1652, 1656, 1660, 1664, 1668, 1672, 1676, 1680, 1684, 1688, 1692, 1696, 1700, 1704, 1707, 1711, 1715, 1719, 1722, 1726, 1729, 1733, 1737, 1741, 1745, 1749, 1753, 1757, 1761, 1765, 1769, 1773, 1777, 1781, 1785, 1789, 1793, 1796, 1800, 1803, 1806, 1809, 1812, 1816, 1820, 1824, 1827, 1831, 1835, 1838, 1841, 1844, 1846, 1850, 1853, 1857, 1861, 1865, 1869, 1873, 1877, 1881, 1885, 1889, 1893, 1897, 1901, 1904, 1908, 1912, 1916, 1920, 1924, 1928, 1932, 1935, 1939, 1943, 1949, 1957, 1961, 1964, 1967, 1970, 1973, 1977, 1981, 1984, 1986, 1988, 1990, 1992, 1994, 1996, 1998; and 1999-2007; (b) the improved trait is selected from the group consisting of larger size, larger seeds, greater yield, darker green color, increased rate of photosynthesis, more tolerance to osmotic stress, more drought tolerance, more heat tolerance, more salt tolerance, more cold tolerance, more tolerance to low nitrogen, early flowering, delayed flowering, more resistance to disease, more seed protein, and more seed oil relative to the control plant.

2.The transgenic plant of claim 1, wherein the conserved domain is at least 80% identical to the conserved domain of the second polypeptide.

Figure 14. Patent claims are appropriating public science at a fast page.

In Summary

The intellectual-property landscape for transformation has shifted. Sponsors of translational research are increasingly interested in clearing IP barriers in advance of making grant awards. And plant-gene patents may become moot, if the Supreme Court rules similarly to their opinion on human genes.

Reference

Chi-Ham CL *et al.* (2012) An intellectual property sharing initiative in agricultural biotechnology: development of broad accessible technologies for plant transformation. Plant Biotechnology Journal 10(5) 501–510.

ALAN BENNETT is professor of plant sciences at the University of California, Davis. He earned BS and PhD degrees in plant biology at UC Davis and Cornell University, respectively, and has over 160 publications. His research has focused on molecular biology of tomato-fruit development and ripening; cell-wall disassembly; and intellectual property rights in agriculture. He is a fellow of the American Association for the Advancement of Science and a senior fellow of the California Council for Science and Technology. He has also served in a range of leadership positions at the University of California, including department chair, divisional associate dean in the College of Agricultural and Environmental Sciences, UC system-wide executive director of research administration and technology transfer, and associate vice chancellor for research at Davis. In these capacities, he has been responsible for research and teaching budgets, for establishing and overseeing research policy, and for the management of a portfolio of over 5,000 patented inventions, 700 active licenses and revenue in excess of $350 million.

In 2004, Dr. Bennett founded the Public Intellectual Property Resource for Agriculture (PIPRA) to accelerate the deployment of public-sector technologies for specialty and subsistence crops in developing countries. PIPRA has been supported by the Rockefeller and Bill & Melinda Gates Foundations as well as by numerous government agencies and private companies.